#86

INVESTIGATIONS IN FISH CONTROL

86. Registration of Thirty-three Fishery Chemicals: Status of Research and Estimated Costs of Required Contract Studies

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(Reports 47 through 50 are in one cover.)

47. Preparation and Properties of Quinaldine Sulfate, an Improved Fish Anesthetic, by John L. Allen and Joe B. Sills. 1973. 7 pp.
48. Toxicity of Quinaldine Sulfate to Fish, by Leif L. Marking and Verdel K. Dawson. 1973. 8 pp.
49. The Efficacy of Quinaldine Sulfate as an Anesthetic for Freshwater Fish, by Philip A. Gilderhus, Bernard L. Berger, Joe B. Sills, and Paul D. Harman. 1973. 9 pp.
50. Residue of Quinaldine in Ten Species of Fish Following Anesthesia with Quinaldine Sulfate, by Joe B. Sills, John L. Allen, Paul D. Harman, and Charles W. Luhning. 1973. 9 pp.

(Reports 51 and 52 are in one cover.)

51. Methods for Simultaneous Determination and Identification of MS-222 and Metabolites in Fish Tissues, by Charles W. Luhning. 1973. 10 pp.
52. Residues of MS-222, Benzocaine, and Their Metabolites in Striped Bass Following Anesthesia, by Charles W. Luhning. 1973. 11 pp.

(Reports 53 through 55 are in one cover.)

53. Toxicity of Mixtures of Quinaldine Sulfate and MS-222 to Fish, by Verdel K. Dawson and Leif L. Marking. 1973. 11 pp.
54. The Efficacy of Quinaldine Sulfate:MS-222 Mixtures for the Anesthetization of Freshwater Fish, by Philip A. Gilderhus, Bernard L. Berger, Joe B. Sills, and Paul D. Harman. 1973. 9 pp.
55. Residues of Quinaldine and MS-222 in Fish Following Anesthesia with Mixtures of Quinaldine Sulfate:MS-222, by Joe B. Sills, John L. Allen, Paul D. Harman, and Charles W. Luhning. 1973. 12 pp.

(Reports 56 through 59 are in one cover.)

56. Toxicity of the Lampricide 3-Trifluoromethyl-4-nitrophenol (TFM) to 10 Species of Algae, by A. A. Maki, L. D. Geissel, and H. E. Johnson. 1975. 17 pp.
57. Acute Toxicites of 3-Trifluoromethyl-4-nitrophenol (TFM) and 2′,5-Dichloro-4′-nitrosalicylanilide (Bayer 73) to Larvae of the Midge *Chironomus tentans,* by J. A. Kawatski, M. M. Ledvina, and C. R. Hansen. 1975. 7 pp.
58. Acute Toxicity of the Lampricide 3-Trifluoromethyl-4-nitrophenol (TFM) to Nymphs of Mayflies (*Hexagenia* sp.), by C. R. Fremling. 1975. 8 pp.
59. Toxicity and Residue Dynamics of the Lampricide 3-Trifluoromethyl-4-nitrophenol (TFM) in Aquatic Invertebrates, by H. O. Sanders and D. F. Walsh. 1975. 9 pp.

(Reports 60 through 62 are in one cover.)

60. Toxicity of the Lampricide 3-Trifluoromethyl-4-nitrophenol (TFM) to Nontarget Fish in Static Tests, by L. L. Marking and L. E. Olson. 1975. 27 pp.
61. Toxicity of the Lampricide 3-Trifluoromethyl-4-nitrophenol (TFM) to Nontarget Fish in Flow-Through Tests, by L. L. Marking, T. D. Bills, and J. H. Chandler Jr.. 1975. 9 pp.
62. Toxicity of the Lampricide 3-Trifluoromethyl-4-nitrophenol (TFM) to Selected Aquatic Invertebrates and Frog Larvae, by J. H. Chandler, Jr. and L. L. Marking. 1975. 7 pp.

(Reports 63 through 66 are in one cover.)

63. Laboratory Efficacy of 3-Trifluoromethyl-4-nitrophenol (TFM) as a Lampricide, by V. K. Dawson, K. B. Cumming, and P. A. Gilderhus. 1975. 13 pp.
64. Effects of 3-Trifluoromethyl-4-nitrophenol (TFM) on Developmental Stages of the Sea Lamprey, by G. W. Piavis and J. H. Howell. 1975. 8 pp.

INVESTIGATIONS IN FISH CONTROL

86. Registration of Thirty-three Fishery Chemicals: Status of Research and Estimated Costs of Required Contract Studies

By R. A. Schnick and F. P. Meyer

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Registration of Thirty-three Fishery Chemicals: Status of Research and Estimated Costs of Required Contract Studies

by

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Abstract

An estimated $8.8 million for contract studies is needed to meet registration requirements for 33 chemicals now used or being considered for use in fish culture and management. Information given for each chemical includes its sponsor, current registration status, research situation in six categories (toxicity to target and nontarget organisms, field testing, physiological studies, analytical methods development, counteraction, and mammalian safety determination), costs of required contract studies, and the prognosis for registration of the use of each compound.

Since Lennon (1967) first issued a warning about the need to register chemicals for fishery use, regulations and guidelines have been developed that require extensive and costly safety evaluation studies (Cumming 1975; U.S. Environmental Protection Agency 1975*a*, 1975*b*). Without these studies, many compounds now being used by fish culturists and fishery managers could become unavailable. If this occurred, the impact on fisheries would be far-reaching: The Great Lakes Fishery Commission estimated that 3.5 million angler days spent each year fishing for lake trout (*Salvelinus namaycush*) and Pacific salmon (*Oncorhynchus* sp.) would be lost if the sea lamprey (*Petromyzon marinus*) were not being controlled by lampricide applications; an estimated 4 million hatchery fish intended for stocking in lakes and streams would be lost if chemicals used for disease treatment were unavailable; and it is anticipated that the $200 million bait and commercial fish culture industry would suffer a 50% or $100 million loss if chemicals were not available for use.

When the U.S. Fish and Wildlife Service (FWS) assigned primary responsibility for facilitating registration of fishery compounds to the Fish Control Laboratory in 1972, the Deputy Associate Director for Research and Environment requested, for each priority compound, a summary of current information regarding its use patterns in fisheries, patent position, status of current registration, and cost estimates of research needed to obtain registration for fishery uses. This information was first presented in status reports on 22 compounds in 1973. Literature reviews on 20 of these compounds were prepared in 1974. Since then, two articles on the registration status of fishery chemicals (Meyer et al. 1976) and on the approaching crisis in the registration of fishery chemicals (Meyer and Schnick 1978) have emphasized the need for mammalian safety data to support registration or reregistration of fishery chemicals. Development of these data requires specialized facilities that are not available within FWS.

We summarize here the research known to have been completed, or yet to be done, on 33 fishery chemicals, based on our interpretation of the requirements and guidelines of regulatory agencies as of January 1978. Information is included on the sponsor of each compound, its current registration status, the research situation in six categories (toxicity to target and nontarget organisms, field testing, physiological studies, analytical methods development, counteraction, and mammalian safety determination), costs for required contract studies, and the prognosis for achieving registration. Requirements for safety evaluation studies on various domestic animals, fish, and wildlife were excerpted from the *Federal Register* (U.S. Environmental Protection Agency 1975*a*). Costs for required work to be done outside FWS are based on January 1978 prices, but will vary among testing facilities. New

rules by FDA governing the laboratory evaluation of the safety of chemicals will probably increase the costs of testing (Smith 1977).

The sequence of the registration procedure is shown in Appendix 1, and the status of research on the various fishery chemicals is summarized in Appendix 2.

Information on each compound was gathered from sponsors, regulatory notices, chemical reference works, literature reviews, and status reports prepared by FWS.

Our estimates of the costs of the contract studies needed to meet registration requirements are $8,839,800, divided as follows:

7 piscicides, lampricides, and collecting aids	$2,954,000
15 therapeutants, disinfectants, pond sterilants, oxidizing agents, and osmoregulatory enhancers	4,239,650
9 herbicides and algicides	1,010,000
2 anesthetics	636,150
Total 33 compounds	$8,839,800

Costs of registering or reregistering chemicals have increased as much as 20-fold in the past 10 years. Under current regulations, registration costs are relatively fixed, whether a product is likely to be widely used and highly profitable or of such limited use that profitability is questionable. FWS encourages industry to accept and bear the major costs of compounds needed in conservation programs, but most chemical companies cannot afford the costs of developing "minor-use" products under present requirements, without outside support.

The Environmental Protection Agency (EPA) recently established a separate committee to give attention to problems concerning registration of minor-use compounds, and the Food and Drug Administration (FDA) is revising the criteria for registration of drugs and biologics needed for minor uses in the production of food animals.

Even though some progress is being made in clarifying procedures and guidelines for registering minor-use compounds, funding has been inadequate to meet the complete research need. In the absence of increased funding for registration research, FWS has had to limit its effort to a few selected priority chemicals at the expense of others. Lack of funds has also made it necessary for FWS to forego the development of new techniques and chemicals.

The following sections provide a synopsis of the current status of the registration for fishery uses of 33 priority chemicals, and the cost of fulfilling existing requirements for safety testing.

Piscicides, Lampricides, and Collecting Aids

Antimycin

Use

Piscicide.

Sponsor

Sold by Aquabiotics Corporation, Northbrook, Ill., under license from the Wisconsin Alumni Research Foundation; Aquabiotics Corp. will not assist in the registration effort.

Registration Status

Registered for nonfood fish use as a piscicide. Studies on antimycin are not being actively pursued by industry. Major studies are needed on mammalian safety, methodology, and residues.

Research Situation

1. Toxicity to target and nontarget organisms: fish — most requirements met; invertebrates and birds — requirements met; plants — requirements partly met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements partly met.
4. Analytical methods development: residues, metabolites, and degradation — requirements partly met.
5. Counteraction: removal and inactivation — most requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); acute dermal, eye, and inhalation studies (rat and rabbit); and 90-day subacute oral (rat) — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. Metabolism (cow)	100,000
3. Metabolism (rat or dog)	25,000
4. 2-year oncogenicity (rat)	100,000
5. 2-year oncogenicity (hamster)	100,000
6. 6-month feeding (dog)	35,000
7. Mutagenicity — Ames test or equivalent	1,500
8. Residues — methodology	120,000
9. Residues — use pattern	40,000
10. Residues — metabolites	60,000
Total	$616,500

Prognosis

Reregistration uncertain. Low concentrations (< 10 parts per billion) ordinarily are used and the material degrades so rapidly under most conditions that sensitive analytical methods with detection limits in parts per trillion are required. Technology for such sensitivity is not now available. Entire registration cost will have to be borne by FWS.

Bayer 73, and the Combination of TFM and Bayer 73

Use

Lampricide; survey tool.

Sponsor

FWS and Great Lakes Fishery Commission. Manufactured by Mobay Chemical Corporation, Kansas City, Mo. (formerly Chemagro), specifically for use as a lampricide. Mobay Chemical Corp. cooperates by allowing FWS to use data in its files.

Registration Status

Registered for nonfood fish use in surveys for larval lampreys and for use as a lampricide in combination with 3-trifluoromethyl-4-nitrophenol (TFM) in the Great Lakes.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and degradation — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal and inactivation — requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); intravenous (iv) or intraperitoneal (ip) injections (rat and mouse); 90-day subacute (rat and hamster); metabolism (cow); and 6-month feeding (dog) — requirements met.
   b. Carcinogenicity and teratology — requirements met.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Reregistration promising. A petition for an exemption from tolerance and an amendment of registration is scheduled to be prepared in fiscal year 1978. Further studies may be needed on the TFM:Bayer 73 mixture.

GD-174

Use

Piscicide.

Sponsor

FWS; owned by McLaughlin Gormley King Co., Minneapolis, Minn. Some technical studies and research are being done by the company.

Registration Status

Not registered for fishery use. GD-174 [2-(digeranylamino)-ethanol] is an experimental compound being tested by FWS as a possible selective control for carp, or as a general piscicide.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements partly met.
2. Field testing: geographic areas, ecotypes, and efficacy — requirements partly met; delivery systems — no work done.
3. Physiological studies: mode of action, biotransformation, and excretion — no work done.
4. Analytical methods development: residues, metabolites, and degradation — requirements partly met.
5. Counteraction: removal and inactivation — requirements partly met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); acute dermal and eye studies (rabbit); 90-day subacute oral (rat and hamster) — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1.	Acute inhalation (rat)	$ 500
2.	21-day subacute dermal (rabbit)	3,000
3.	Teratology (rabbit)	35,000
4.	Metabolism (cow)	100,000
5.	Metabolism (rat or dog)	25,000
6.	2-year oncogenicity (rat)	100,000
7.	2-year oncogenicity (hamster)	100,000
8.	6-month feeding (dog)	35,000
9.	Avian acute oral (three species)	5,000
10.	1-generation reproduction (bobwhite quail or mallard)	20,000
11.	Residues — methodology	60,000
12.	Residues — use pattern	40,000
13.	Residues — metabolites	60,000
	Total	$583,500

Prognosis

Registration uncertain. Field studies have indicated that GD-174 is an excellent piscicide but have failed to duplicate the selective action against carp noted in laboratory studies. GD-174 has phytotoxic properties but these should not be a serious obstacle to registration. Should either rotenone or antimycin be lost to fishery use, GD-174 is an excellent candidate replacement.

Rotenone

Use

Piscicide.

Sponsor

S. B. Penick & Co., Lyndhurst, N.J., and others.

Registration Status

Registered for nonfood fish use as a piscicide. S. B. Penick & Co. is negotiating with EPA to resolve the problem of a Rebuttable Presumption Against Registration listing caused by a Spanish report which supposedly showed that rotenone is carcinogenic when injected into rats. A study was initiated by EPA to determine whether the Spanish results could be duplicated. Available results to date show no carcinogenicity. A hamster study was terminated because high mortality of control animals made the test results statistically invalid. The master study is being repeated.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements partly met.
4. Analytical methods development: residues, metabolites, and degradation — requirements partly met.
5. Counteraction: removal and inactivation — requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); 2-year feeding (rat); and acute dermal, eye, and inhalation studies — requirements met.
   b. Carcinogenicity and teratology; 2-year oncogenicity (hamster) — in progress.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. Metabolism (cow)	100,000
3. Metabolism (rat)	25,000
4. 2-year oncogenicity (rat)	100,000
5. 6-month feeding (dog)	35,000
6. Mutagenicity — Ames test or equivalent	1,500
7. Residues — methodology	120,000
8. Residues — use pattern	40,000
9. Residues — metabolites	180,000
Total	$636,500

Prognosis

Reregistration uncertain. S. B. Penick & Co. is highly interested in maintaining the registration of rotenone as a piscicide, and is willing to perform some of the needed residue and safety studies.

Squoxin

Use

Piscicide.

Sponsor

American Cyanamid Co., Princeton, N.J.; assisted by the National Marine Fisheries Service.

Registration Status

Not registered for fishery use. EPA has granted a yearly renewable permit for field tests for use as a selective toxicant for squawfish.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements partly met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action and excretion — requirements partly met; biotransformation — no work done.
4. Analytical methods development: residues, metabolites, and degradation — requirements partly met.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); dermal toxicity (rabbit); and 31-day subacute oral (rat) — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. 90-day subacute oral (rat)	25,000
2. 90-day subacute oral (dog)	25,000
3. Teratology (rabbit)	35,000
4. Metabolism (cow)	100,000

5. Metabolism (rat)	25,000
6. 2-year oncogenicity (rat)	100,000
7. 2-year oncogenicity (hamster)	100,000
8. 6-month feeding (dog)	35,000
9. Mutagenicity — Ames test or equivalent	1,500
10. Avian acute oral (mallard or quail)	1,500
11. 8-day avian subacute dietary (bobwhite quail or pheasant)	1,000
12. Residues — methodology	15,000
13. Residues — use pattern	10,000
14. Residues — metabolites	60,000
Total	$534,000

Prognosis

Registration uncertain. Currently completed studies are not adequate to meet EPA requirements for registration. Safety evaluation and residue data must be developed before the compound can be registered.

TFM

Use

Lampricide.

Sponsor

FWS and Great Lakes Fishery Commission; manufactured by American Hoechst Corp., Somerville, N.J.

Registration Status

Registered for nonfood fish use as a lampricide.

In February 1976 FWS submitted petitions for an exemption from tolerance and an amendment of registration for use of the sodium salt of TFM (3-trifluoromethyl-4-nitrophenol) as a lampricide. EPA provided preliminary comments on 22 October 1976, to which FWS responded. Further comments from EPA were received in March and April 1977.

Data provided were adequate to support negotiations that eliminated the need for further studies in several categories: acute oral toxicity tests; 2-year hamster feeding study; characterization of residues in milk, cattle kidney, and other edible products of cultured mammals; and an indication of the distribution, retention, or elimination of TFM and its metabolites.

Points still being negotiated include an exemption for the application of dimethylformamide in streams as a part of TFM formulations, residue information in potable waters, possible restrictions on use in irrigation waters, and possible soil binding effects. An Ames test to evaluate potential mutagenicity of TFM was completed and found negative by Wisconsin Alumni Research Foundation. Progress continues toward registration.

Research Situation

All research studies originally required have been completed.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Reregistration highly promising. Outlook is excellent for continued and amended registration and for exemption from tolerance.

Thanite

Use

Collecting aid; piscicide.

Sponsor

FWS; owned by McLaughlin Gormley King Co., Minneapolis, Minn.

Registration Status

Not registered for fishery use. Thanite is an experimental fish collecting aid. EPA will require additional oncogenic data for reregistration of its current label as an insecticide.

Research Situation

1. Toxicity to target and nontarget organisms: fish — most requirements met; invertebrates and birds — requirements partly met; plants — no work done.
2. Field testing: geographic areas and ecotypes — requirements met; efficacy and delivery systems — requirements partly met.
3. Physiological studies: mode of action — requirements met; biotransformation and excretion — no work done.
4. Analytical methods development: residues and metabolites — requirements partly met; degradation — no work done.
5. Counteraction: removal and inactivation — requirements partly met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat, rabbit, and guinea pig); 6-month subacute oral (rat and guinea pig); and acute dermal and inhalation studies — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. 90-day subacute oral (hamster)	$ 25,000
2. Teratology (rabbit)	35,000
3. Metabolism (cow)	100,000

4. Metabolism (rat) 25,000
5. 2-year oncogenicity (rat) 100,000
6. 2-year oncogenicity (hamster) 100,000
7. 6-month feeding (dog) 35,000
8. Mutagenicity — Ames test or equivalent 1,500
9. 8-day avian subacute (mallard) 1,000
10. 8-day avian subacute (quail or pheasant) 1,000
11. Residues — methodology 60,000
12. Residues — use pattern 40,000
13. Residues — metabolites 60,000

Total $583,500

Prognosis

Registration unlikely. Research has been halted. McLaughlin Gormley King Co. has expressed concern over the cost of the mammalian safety tests that will be required and has decided not to continue efforts toward obtaining a registration for fishery use at this time.

Therapeutants, Disinfectants, Pond Sterilants, Oxidizing Agents, and Osmoregulatory Enhancers

Betadine

Use

Therapeutant.

Sponsor

Purdue Frederick Company, Norwalk, Conn.

Registration Status

Not registered for fishery use. National Institute for Occupational Safety and Health has expressed concern because a portion of the molecule (poly[1-vinyl-2-pyrrolidinone], polymer no. 1) has produced tumors in rats in experimental studies.

Research Situation

Requirements are considered to have been met, except perhaps for bird toxicity.

Costs for Required Work to be Done Outside FWS

1. Mutagenicity — Ames test or equivalent $1,500
2. 8-day avian subacute dietary (mallard) 1,000
3. 8-day avian subacute dietary (quail or pheasant) 1,000

Total $3,500

Prognosis

Registration highly promising. Betadine is registered as a disinfectant for human and animal skin. Purdue Frederick Co., in conjunction with Tavolek, Inc., is preparing a New Animal Drug Application on Betadine for use as a fish egg disinfectant. Most of the required research is considered complete on Betadine.

Calcium Hypochlorite (HTH)

Use

Disinfectant.

Sponsor

Olin Corporation, Stamford, Conn.

Registration Status

Registered for fishery use as a disinfectant; for sanitizing fish tanks, raceways, and utensils; and for controlling algae and bacteria in fish ponds.

Research Situation

No additional research needed.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Desired registration has been achieved.

Formalin

Use

Therapeutant.

Sponsor

FWS; manufactured and sold by many companies.

Registration Status

Not registered for fishery use. Formalin is used extensively by fish culturists as a therapeutant for external parasites on fish and fungus on fish eggs. National Institute for Occupational Safety and Health has expressed concern because neoplastic effects were observed in rats.

Research Situation

Required studies completed to date are considered to be adequate. FDA may require that further tests be done.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit) $35,000

Prognosis

Registration highly promising. A Not New Drug

Monograph was submitted to FDA in 1973. On the basis of the review of this document, FDA ruled that residue studies based on the use pattern would have to be carried out. The Fish Control Laboratory completed such studies and submitted the information to FDA in 1977.

Furanace

Use
Therapeutant.

Sponsor
Abbott Laboratories, North Chicago, Ill. The company has expressed a willingness to help support some of the required research. Zodiac Pet Products, Inc., Dallas, Texas, currently markets the compound for aquarium use.

Registration Status
Registered for nonfood fish use. Abbott Laboratories obtained an aquarium use registration for Furanace in December 1975. A petition for food fish use submitted by Abbott to FDA in 1976 was denied, pending submission of additional data.

Research Situation
1. Toxicity to target and nontarget organisms: fish and invertebrates — requirements met; birds and plants — not needed.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: host responses and mode of action — requirements met; biotransformation and excretion — no work done.
4. Analytical methods development: residues — most requirements met; metabolites and degradation — no work done.
5. Counteraction: removal and inactivation — requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); and 120-day subacute oral (mice) — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. Acute dermal (rabbit)	$ 300
2. Acute dermal irritation (rabbit)	150
3. Acute eye irritation (rabbit)	200
4. Acute inhalation (rat)	500
5. 90-day subacute oral (dog)	25,000
6. Teratology (rabbit)	35,000
7. 2-year oncogenicity (rat)	100,000
8. 2-year oncogenicity (hamster)	100,000
9. 6-month feeding (dog)	35,000
10. Mutagenicity — Ames test or equivalent	1,500
11. Residues — methodology	40,000
12. Residues — use pattern	40,000
13. Residues — metabolites	60,000
Total	$437,650

Prognosis
Food use registration uncertain. Many of the above tests may not be needed if FDA accepts the removal of Furanace by filtration of treated water through carbon, or establishes new minor-use requirements. Current label for use on aquarium fishes could easily be expanded to include nonfood fishes. Inclusion of food fishes will require completion of listed research or changes in FDA position, as indicated above.

Furazolidone

Use
Therapeutant.

Sponsor
Hess and Clark, Division of Rhodia, Inc., Ashland, Ohio.

Registration Status
Not registered for fishery use.

Research Situation
1. Toxicity to target and nontarget organisms: fish — requirements partly met; invertebrates and plants — no work done; birds — requirements met.
2. Field testing: geographic areas, ecotypes — no work done; efficacy — requirements partly met; delivery systems — no work done.
3. Physiological studies: host responses, mode of action, biotransformation, and excretion — no work done.
4. Analytical methods development: residues and metabolites — requirements partly met; degradation — no work done.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); 53-week feeding (rat); and ip injection studies — requirements met.
   b. Carcinogenicity and teratology: 2-year oncogenicity (rat and mouse) — requirements met.

Costs for Required Work to be Done Outside FWS

1.	Teratology (rabbit)	$ 35,000
2.	Metabolism (cow)	100,000
3.	Metabolism (rat)	25,000
4.	6-month feeding (dog)	35,000
5.	Residues — methodology	40,000
6.	Residues — use pattern	40,000
7.	Residues — metabolites	40,000
	Total	$315,000

Prognosis

Registration highly unlikely. A notice of intent by FDA to cancel registrations for furazolidone appeared 13 May 1976 in the *Federal Register*. This course of action is being considered because of the potential carcinogenic or mutagenic action of the compound. Chances of having the compound approved for fishery use are nil.

Hyamine 1622

Use

Therapeutant; disinfectant.

Sponsor

Rohm and Haas Co., Philadelphia Pa.

Registration Status

Not registered for fishery use. Hyamine 1622 has potential use as a disinfectant and as a treatment for bacterial gill disease. The compound was dropped from consideration in 1973 because the product is a mixture of compounds, and complex residue studies would be required. Also, Furanace was considered to be a better choice as a control for bacterial gill disease. Research was resumed on the product in 1978 because of renewed interest in the compound by fish culturists.

Research Situation

1. Toxicity to target and nontarget organisms: fish — requirements partly met; invertebrates, birds, and plants — no work done.
2. Field testing: geographic areas and ecotypes — no work done; efficacy and delivery systems — requirements partly met.
3. Physiological studies: host responses, mode of action, biotransformation and excretion — no work done.
4. Analytical methods development: residues — requirements partly met; metabolites and degradation — no work done.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat and mouse); 1-year feeding (dog); 2-year feeding (rat); and acute dermal and eye studies; iv or ip injections — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1.	Teratology (rabbit)	$ 35,000
2.	Metabolism (cow)	100,000
3.	Metabolism (rat)	25,000
4.	2-year oncogenicity (rat)	100,000
5.	2-year oncogenicity (hamster)	100,000
6.	Residues — methodology	100,000
7.	Residues — use pattern	40,000
8.	Residues — metabolites	60,000
	Total	$560,000

Prognosis

Registration uncertain. Too few data are available to evaluate potential problems in registering Hyamine 1622. The fact that the product is a mixture of compounds may complicate registration efforts.

Lime (Calcium Carbonate, Calcium Hydroxide, and Calcium Oxide)

Use

Pond sterilant.

Sponsor

FWS.

Registration Status

Registered for fishery use as a pond sterilant under the Generally Recognized As Safe classification.

Research Situation

Requirements met.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Desired registration has been achieved.

Malachite Green, and the Combination of Malachite Green and Formalin

Use

Therapeutant.

Sponsor

FWS; produced by American Cyanamid Co., Princeton, N.J., and others.

Registration Status

Not registered for fishery use. Malachite green is used extensively to control fungi and protozoans. In combination with formalin it is very effective against *Ichthyophthirius* infections.

Research Situation

1. Toxicity to target and nontarget organisms: fish and invertebrates — requirements met; birds — not needed; plants — requirements partly met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: host responses and excretion — requirements partly met; mode of action — requirements met; biotransformation — no work done.
4. Analytical methods development: residues — requirements partly met; metabolites and degradation — no work done.
5. Counteraction: removal — requirements met; inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); iv or ip injections — requirements met.
   b. Carcinogenicity and teratology: teratology (rabbit) — requirements met.

Costs for Required Work to be Done Outside FWS

1. 90-day subacute oral (rat)	$ 25,000
2. 90-day subacute oral (dog)	25,500
3. Teratology (F_3 generation rat)	100,000
4. Metabolism (cow)	100,000
5. Metabolism (rat)	25,000
6. 2-year oncogenicity, parent compound (rat)	100,000
7. 2-year oncogenicity, parent compound (mouse)	100,000
8. 3-generation reproduction, parent compound (rat)	100,000
9. 2-year oncogenicity, metabolites (rat)	100,000
10. 2-year oncogenicity, metabolites (mouse)	100,000
11. 3-generation reproduction, metabolites (rat)	100,000
12. 6-month feeding (dog)	35,000
13. Mutagenicity — Ames test or equivalent	1,500
14. Residues — methodology	200,000
15. Residues — use pattern	40,000
16. Residues — metabolites	400,000
Total	$1,552,000

Prognosis

Registration highly unlikely. Malachite green has been implicated as a possible teratogen and carcinogen in fish, and a study in rabbits showed some teratology. Discussions with FDA officials indicated that the full complement of safety tests would be required. Even if all the studies were performed, no guarantee could be given that malachite green could be registered. FWS has halted its efforts to register it.

Masoten (Trichlorfon)

Use

Therapeutant.

Sponsor

Bayvet Division of Mobay Chemical Corp., Kansas City, Mo.

Registration Status

Registered for nonfood fish use. Masoten is used in fisheries as a control for a variety of ectoparasites, especially the anchor parasite, *Lernaea.* National Institute for Occupational Safety and Health has expressed concern because it has produced carcinogenic effects on animals in two studies and teratogenic effects in another.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: host responses, mode of action, excretion, and biotransformation — requirements partly met.
4. Analytical methods development: residues and degradation — requirements met; metabolites — no work done.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); ip injections; 90-day subacute (rat); and 2-year feeding (rat and dog) — requirements met.
   b. Carcinogenicity and teratology — requirements met.

Costs for Required Work to be Done Outside FWS

1. Residues — metabolites	$75,000

Prognosis

Registration for use on food fish unlikely. Masoten is subject to Rebuttable Presumption Against Registration and its status is uncertain. If it is not canceled for other uses and if a food use is desired, the listed tests will probably be required. The company has shown little interest in extending the label to food fish use.

Nitrofurazone (Furacin)

Use

Therapeutant.

Sponsor

FWS; sold by Norwich Pharmacal Co., Norwich, N.Y.

Registration Status

Not registered for fishery use. Nitrofurazone was listed as a drug of concern in an FDA notice of intent to cancel registration of furazolidone because of its possible carcinogenicity or mutagenicity. Nitrofurazone is considered a close analog of furazolidone.

Research Situation

1. Toxicity to target and nontarget organisms: fish and birds — requirements partly met; invertebrates and plants — no work done.
2. Field testing: geographic areas and ecotypes — no work done; efficacy and delivery systems — requirements partly met.
3. Physiological studies: host responses, mode of action, biotransformation, and excretion — no work done.
4. Analytical methods development: residues and degradation — requirements partly met; metabolites — no work done.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); 53-week feeding (rat); skin tests; and ip injections — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. 90-day subacute (dog)	$ 25,000
2. Teratology (rabbit)	35,000
3. Metabolism (cow)	100,000
4. Metabolism (rat)	25,000
5. 2-year oncogenicity (hamster)	100,000
6. 2-year oncogenicity (rat)	100,000
7. 6-month feeding (dog)	35,000
8. Residues — methodology	40,000
9. Residues — use pattern	40,000
10. Residues — metabolites	40,000
Total	$540,000

Prognosis

Registration highly unlikely. Because of the concern over the possible carcinogenicity of nitrofurans, it is unlikely that any fishery uses of nitrofurazone could be registered unless such concern is favorably resolved.

Potassium Permanganate

Use

Oxidizing agent.

Sponsor

FWS; sold by Carus Chemical Company, Inc., La Salle, Ill.

Registration Status

Not registered for fishery use.

Research Situation

1. Toxicity to target and nontarget organisms: fish — requirements met; invertebrates and plants — requirements partly met; birds — no work done.
2. Field testing: geographic areas and ecotypes — requirements partly met; efficacy — requirements met; delivery systems — requirements partly met.
3. Physiological studies: host responses and mode of action — requirements partly met; biotransformation and excretion — no work done.
4. Analytical methods development: residues — requirements partly met; metabolites — no work done; degradation — requirements met.
5. Counteraction: removal and inactivation — requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); acute subcutaneous (mouse); and acute dermal and eye studies — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. 90-day subacute oral (rat)	$ 25,000
2. 90-day subacute oral (dog)	25,000
3. Teratology (rabbit)	35,000
4. Metabolism (cow)	100,000
5. Metabolism (rat)	25,000
6. 2-year oncogenicity (rat)	100,000
7. 2-year oncogenicity (hamster)	100,000
8. 6-month feeding (dog)	35,000
9. Residues — methodology	40,000
10. Residues — use pattern	40,000
11. Residues — metabolites	60,000
Total	$585,000

Prognosis

Registration promising. Since certain fishery uses of potassium permanganate are not considered to be pesticidal, a petition for exemption from registration has been requested. If the exemption is not allowed, many of the above tests will be required.

R05-0037 (Sulfadimethoxine and Ormetoprim)

Use
Therapeutant.

Sponsor
Hoffmann-La Roche, Inc., Nutley, N.J.

Registration Status
Not registered for fishery use. A decision was made to drop this sulfa drug in 1974 because the potentiator leaves residues in fish skin. A nitrofuran such as furazolidone or nitrofurazone was suggested as a suitable substitute, but these have been dropped because they are considered to be potential carcinogens. R05-0037 was reconsidered for registration in 1977.

Research Situation
1. Toxicity to target and nontarget organisms: fish and birds — requirements met; invertebrates and plants — requirements partly met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements partly met.
3. Physiological studies: host responses and excretion — requirements partly met; mode of action — requirements met; biotransformation — no work done.
4. Analytical methods development: residues and metabolites — requirements partly met; degradation — no work done.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (mouse); 13-week subacute oral (rat and dog); and 9-week subacute oral (pig) — requirements met.
   b. Carcinogenicity and teratology: teratology (dog) — requirements met.

Costs for Required Work to be Done Outside FWS

1. Metabolism (cow)	$100,000
2. Metabolism (rat)	25,000
3. Mutagenicity — Ames test or equivalent	1,500
4. Residues — use pattern	10,000
Total	$136,500

Prognosis
Registration promising. The sponsoring company apparently is interested in the compound and will pursue its registration. Potential problems exist because skin tissues may retain residues of the drug for extended periods. Withdrawal requirements could be as long as 6 months after use. Efficacy studies are under way to determine if a shorter treatment period would result in a shorter residue retention period.

Sodium Chloride

Use
Osmoregulatory enhancer.

Sponsor
FWS.

Registration Status
Registered for fishery use as an osmoregulatory enhancer under the Generally Recognized as Safe registration.

Research Situation
Requirements met.

Costs for Required Work to be Done Outside FWS
None; requirements met.

Prognosis
Desired registration has been achieved.

Sulfamerazine

Use
Therapeutant.

Sponsor
FWS and American Cyanamid Co., Princeton, N.J.

Registration Status
Registered for food fish use. Sulfamerazine is registered for the treatment of furunculosis in trout and salmon only.

Research Situation
No research is under way to extend the use label. Known research needs have been met.

Costs for Required Work to be Done Outside FWS
None; requirements met.

Prognosis
Reregistration promising. No problems are anticipated when reregistration is required.

Terramycin

Use
Therapeutant.

Sponsor
FWS and Pfizer, Inc., New York, N.Y.

Registration Status

Registered for food fish use. Terramycin is registered for treatment of bacterial infections in trout, salmon, and catfish and for marking bones or scales of fish in age or identification studies.

Research Situation

No research is under way to extend the label. Known research needs have been met.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Reregistration promising. No problems are anticipated when reregistration is required unless Terramycin is restricted to human uses only. Such a restriction has been rumored because of the possible transfer of resistance factors between pathogenic and nonpathogenic bacteria. Current FDA concerns relate only to subtherapeutic uses. Since fishery uses involve only therapeutic levels, it appears that the compound will remain available.

Herbicides and Algicides

Copper Sulfate

Use

Herbicide and algicide.

Sponsor

Cities Service Co., Atlanta, Ga.; Phelps Dodge Refining Corp., New York, N.Y.; 3M Company, St. Paul, Minn.; and others.

Registration Status

Registered for food fish use. Two types of tolerances exist for copper as an active component of algicides: exemptions from tolerance exist for $CuSO_4{:}5H_2O$ and basic copper carbamate, and finite tolerances of 1 ppm have been established for copper complexes.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal — requirements met; inactivation — requirements partly met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity — requirements met.
   b. Carcinogenicity and teratology — requirements met.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Desired registration has been achieved. Manufacturers of copper sulfate (Kennecot Chemical, 3M Company, and Phelps Dodge Refining Corp.) indicated to the Fish Control Laboratory that they were not interested in attempting to register copper sulfate for other uses.

2,4-D

Use

Herbicide.

Sponsor

AmChem Products, Inc., Ambler, Pa.; Dow Chemical USA, Midland, Mich.; and others.

Registration Status

Registered for food fish use. It can be used as an herbicide only by Federal, State, or local public agencies.

Research Situation

All requirements are considered met, except counteraction.

Costs for Required Work to be Done Outside FWS

None; requirements met.

Prognosis

Extended registration uncertain. Efforts are being made by AmChem Products, Inc. to extend the use of 2,4-D to other than public agencies. Contract studies have been started by the company.

Dichlobenil

Use

Herbicide.

Sponsor

Thompson-Hayward Chemical Co., Kansas City, Kans.

Registration Status

Registered for nonfood fish use. Dichlobenil can be

used in ponds, lakes, and reservoirs with nonflowing waters, but the fish cannot be used for food or feed for 90 days after application. The herbicide cannot be used in waters open to commercial fishing for fish or shellfish. EPA will require additional data on oncogenic properties for reregistration.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues — requirements met; metabolites and degradation — requirements partly met.
5. Counteraction: removal and inactivation — most requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity — requirements met.
   b. Carcinogenicity and teratology: 2-year oncogenicity (rat) — requirements met.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. 2-year oncogenicity (hamster)	100,000
Total	$135,000

Prognosis

Registration for food fish use unlikely. No known effort is under way to extend the label for food fish use.

Diquat

Use

Herbicide.

Sponsor

Chevron Chemical Co., San Francisco, Calif.

Registration Status

Registered for food fish use. EPA allows residues of diquat in potable water during the review of the petition for tolerance. EPA will require additional oncogenic data for reregistration.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal and inactivation — requirements met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); 2-year feeding (rat and dog); and acute dermal, eye, and inhalation studies — requirements met.
   b. Carcinogenicity and teratology: teratology (rat); and histopathological and neuropathological studies on chronic test animals — requirements met.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. 2-year oncogenicity (rat)	100,000
3. 2-year oncogenicity (hamster)	100,000
Total	$235,000

Prognosis

Reregistration promising. No problems are anticipated when reregistration is required.

Diuron

Use

Herbicide.

Sponsor

AmChem Products, Inc., Ambler, Pa.; E. I. Dupont De Nemours & Co., Inc., Wilmington, Del.

Registration Status

Not registered for fishery use. It is registered in the United States for treating irrigation ditches only and has an aquatic use registration in Canada. EPA will require additional oncogenic data for reregistration.

Research Situation

All research has been completed except for counteraction and teratology studies.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$35,000

Prognosis

Registration unlikely. There is a tolerance in meat of mammals, but diuron accumulates in fish tissues.

Endothall

Use

Herbicide.

Sponsor
Pennwalt Corp., Fresno, Calif.

Registration Status
Registered for food fish use. Endothall was given an interim food additive tolerance covering use in canals, lakes, ponds, or other potential sources of potable water in 1973.

Research Situation
1. Toxicity to target and nontarget organisms: fish, birds, invertebrates, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal — requirements met; inactivation — requirements partly met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity — requirements met.
   b. Carcinogenicity and teratology: life-time oncogenicity (mouse); teratology (rat) — requirements met.

Costs for Required Work to be Done Outside FWS
None; requirements met.

Prognosis
Reregistration promising. No problems are anticipated when reregistration is required.

Fenac

Use
Herbicide.

Sponsor
AmChem Products, Inc., Ambler, Pa.; and others.

Registration Status
Registered for nonfood fish use. Fenac is registered for use in lakes, drainage ditches, ponds, and reservoirs where the water is not used for irrigation or domestic purposes or for livestock. EPA will require additional oncogenic data for reregistration.

Research Situation
1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat); chronic feeding (rat and dog); and acute dermal, eye, and inhalation studies — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. 2-year oncogenicity (rat)	100,000
3. 2-year oncogenicity (hamster)	100,000
Total	$235,000

Prognosis
Extended registration uncertain. AmChem Products, Inc. would like to obtain a label for more generalized use, but is pursuing an extension of 2,4-D labels first.

Silvex

Use
Herbicide.

Sponsor
Dow Chemical USA, Midland, Mich.; and others.

Registration Status
Registered for nonfood fish use. Silvex can be used in lakes and ponds to control emergent or submersed vegetation, but cannot be used where it could contaminate water intended for domestic use, irrigation, or crop spraying.

Research Situation
1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal — most requirements met; inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity — requirements met.

b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. 2-year oncogenicity (rat)	100,000
3. 2-year oncogenicity (hamster)	100,000
Total	$235,000

Prognosis

Food use registration uncertain. No known research is under way to extend the label for food use. Silvex is a candidate for the Rebuttable Presumption Against Registration list.

Simazine

Use

Herbicide.

Sponsor

Ciba-Geigy Corp., Greensboro, N.C.

Registration Status

Registered for food fish use. Simazine has a tolerance of 0.1 ppm in potable water and 12 ppm in agricultural commodity fish. The registration allows use of simazine in ponds (single owner and little or no outflow). An experimental use permit was granted for experiments on algae in lakes in 1975. EPA will require additional oncogenic data for reregistration.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal — most requirements met; inactivation — requirements partly met.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity — requirements met.
   b. Carcinogenicity and teratology: 2-year oncogenicity (rat) — requirements met.

Costs for Required Work to be Done Outside FWS

1. Teratology (rabbit)	$ 35,000
2. 2-year oncogenicity (hamster)	100,000
Total	$135,000

Prognosis

Extended registration uncertain. The compound may require more research.

Anesthetics

MS-222 (Tricaine Methanesulfonate)

Use

Anesthetic.

Sponsor

Ayerst Laboratories, New York, N.Y., and others.

Registration Status

Registered for food fish use as an anesthetic; 21-day withdrawal period required after use on food fish.

Research Situation

1. Toxicity to target and nontarget organisms: fish, invertebrates, birds, and plants — requirements met.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal — requirements met; inactivation — not needed.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity — not needed.
   b. Carcinogenicity and teratology — not needed.

Costs for Required Work to be Done Outside FWS

1. Mutagenicity — Ames test or equivalent	$1,500

Prognosis

Desired registration has been achieved. Further research will be directed toward reducing the 21-day withdrawal time.

Quinaldine Sulfate, and the Combination of MS-222 and Quinaldine Sulfate

Use

Anesthetic.

Sponsor

FWS; a possible producer is McLaughlin Gormley King Co., Minneapolis, Minn.

Registration Status

Not registered for fishery use.

Research Situation

1. Toxicity to target and nontarget organisms: fish — requirements met; invertebrates and plants — not needed; birds — no work done.
2. Field testing: geographic areas, ecotypes, efficacy, and delivery systems — requirements met.
3. Physiological studies: mode of action, biotransformation, and excretion — requirements met.
4. Analytical methods development: residues, metabolites, and degradation — requirements met.
5. Counteraction: removal and inactivation — no work done.
6. Mammalian safety determination:
   a. Acute, subacute, and chronic toxicity: acute oral LD_{50} (rat) — requirements met.
   b. Carcinogenicity and teratology — no work done.

Costs for Required Work to be Done Outside FWS

1. Acute dermal (rabbit)	$ 300
2. Acute primary dermal irritation (rabbit)	150
3. Acute primary eye irritation (rabbit)	200
4. Acute inhalation (rat)	500
5. 90-day subacute oral (rat)	25,000
6. 90-day subacute oral (dog)	25,000
7. Teratology (rabbit)	35,000
8. Metabolism (cow)	100,000
9. Metabolism (rat)	25,000
10. 2-year oncogenicity (rat)	100,000
11. 2-year oncogenicity (hamster)	100,000
12. 6-month feeding (dog)	35,000
13. Mutagenicity — Ames test or equivalent	1,500
14. Avian acute oral (three species)	5,000
15. 8-day avian subacute dietary (mallard)	1,000
16. 8-day avian subacute dietary (quail or pheasant)	1,000
17. 1-generation reproduction (bobwhite quail or mallard)	20,000
18. Residues — methodology	60,000
19. Residues — use pattern	40,000
20. Residues — metabolites	60,000
Total	$634,650

Prognosis

Registration promising. McLaughlin Gormley King Co. has expressed interest in supporting a limited amount of the needed research. After reviewing New Animal Drug Applications for quinaldine sulfate and the combination of quinaldine sulfate and MS-222 submitted by FWS in 1974, FDA required additional research for consideration of a registration for food fish use. Some contract studies on this compound may not be needed if FDA waives certain of its requirements.

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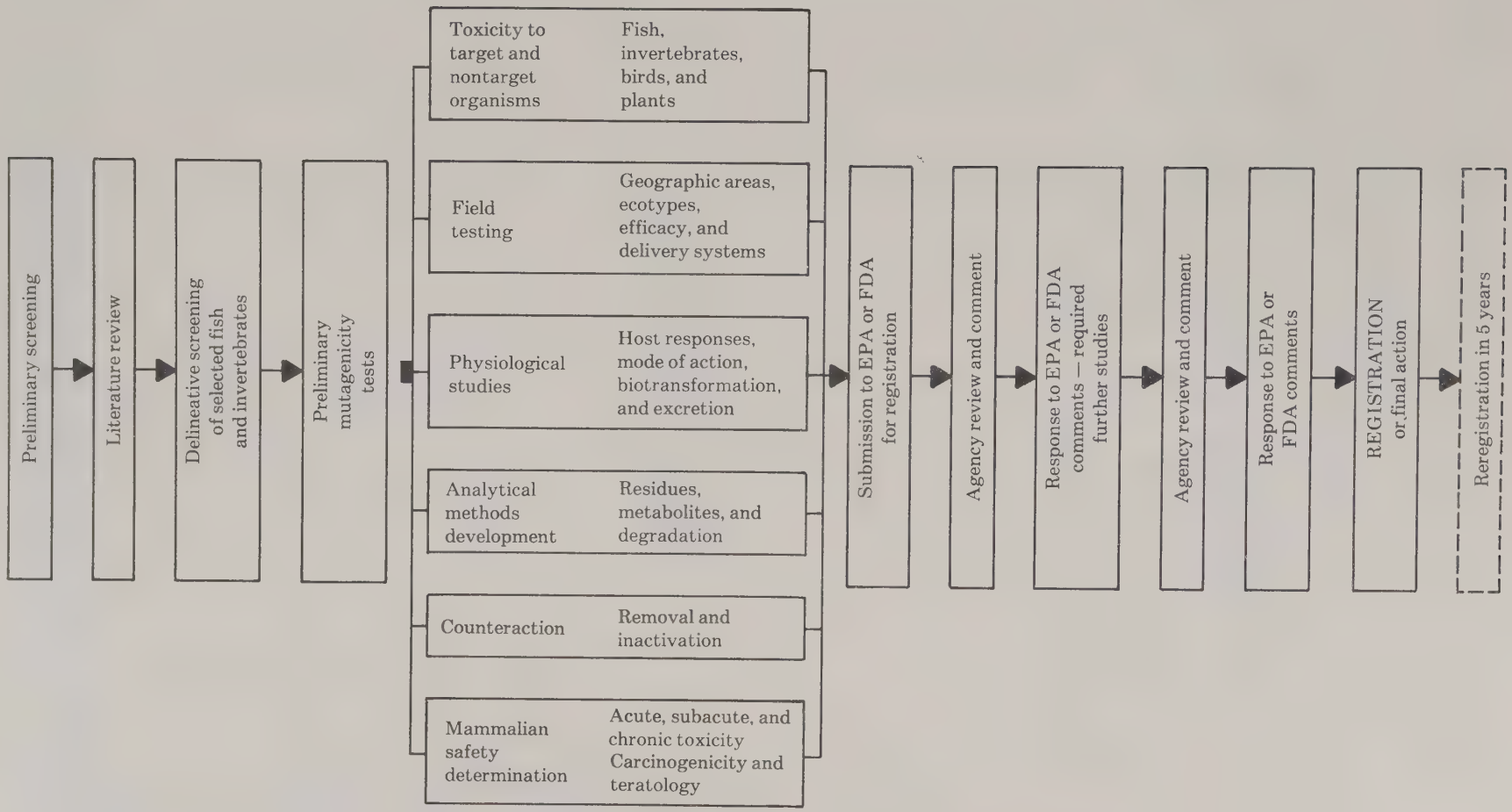
Appendix 1. *Flow chart of activities required for the registration of fishery chemicals by the Environmental Protection Agency (EPA) or by the Food and Drug Administration (FDA).*


Preliminary screening
Literature review
Delineative screening of selected fish and invertebrates
Preliminary mutagenicity tests
Toxicity to target and nontarget organisms
Fish, invertebrates, birds, and plants
Field testing
Geographic areas, ecotypes, efficacy, and delivery systems
Physiological studies
Host responses, mode of action, biotransformation, and excretion
Analytical methods development
Residues, metabolites, and degradation
Counteraction
Removal and inactivation
Mammalian safety determination
Acute, subacute, and chronic toxicity Carcinogenicity and teratology
Submission to EPA or FDA for registration
Agency review and comment
Response to EPA or FDA comments — required further studies
Agency review and comment
Response to EPA or FDA comments
REGISTRATION or final action
Reregistration in 5 years

Appendix 2. *Status of research on fishery chemicals, January 1978 (c = complete, pc = partly complete; o = no work done).*

	Research and development categories										
	Preliminary investigations	Preliminary mutagenicity tests	Toxicity to non-target organisms	Field tests	Physiological studies	Analytical methods and residues	Counteraction	Mammalian safety — acute, subacute, chronic toxicity	Mammalian safety — developmental problems	Submissions to FDA or EPA[a]	Comment or situation[a]
Piscicides, lampricides, or collecting aids											
Antimycin	c	o	pc	c	pc	pc	pc	pc	o	c	Registered by EPA
Bayer 73	c	c	c	c	c	c	c	c	c	o	Ready for submission to EPA
GD-174	c	c	pc	pc	o	pc	pc	pc	o	o	Experimental use only
Rotenone	c	c	c	c	pc	pc	c	pc	pc	c	On RPAR list
Squoxin	c	o	pc	c	pc	pc	o	pc	o	o	Being sponsored by NMFS
TFM	c	c	c	c	c	c	c	c	c	c	Awaiting final action by EPA
Thanite	c	o	pc	pc	pc	pc	pc	pc	o	o	Research discontinued
Therapeutants, disinfectants, pond sterilants, oxidizing agents, and osmoregulatory enhancers											
Betadine	c	o	pc	c	c	c	c	c	c	o	Ready for submission to FDA
Calcium hypochlorite	c	c	c	c	c	c	c	c	c	c	Registered by EPA
Formalin	c	c	c	c	c	c	c	c	pc	c	Awaiting final action by FDA
Furanace	c	o	c	c	pc	pc	c	pc	o	o	Responding to FDA comments for use on food fish
Furazolidone	c	c	pc	pc	o	pc	o	pc	pc	o	Notice to cancel filed by FDA
Hyamine 1622	c	c	pc	pc	o	pc	o	pc	o	o	Research renewed in 1977
Lime	c	c	c	c	c	c	c	c	c	c	GRAS
Malachite green	c	o	pc	c	pc	pc	pc	pc	pc	o	Research terminated
Masoten	c	c	c	c	pc	pc	o	pc	c	c	Nonfood use only, on RPAR list
Nitrofurazone	c	c	pc	pc	o	pc	o	pc	o	o	FDA may cancel
Potassium permanganate	c	c	pc	pc	pc	pc	pc	pc	o	c	Awaiting ruling by EPA
R05-0037	c	o	pc	pc	pc	pc	o	pc	c	o	Experimental use only

Appendix 2. Continued. *Status of research on fishery chemicals, January 1978 (c = complete, pc = partly complete; o = no work done).*

	Research and development categories										
	Preliminary investigations	Preliminary mutagenicity tests	Toxicity to non-target organisms	Field tests	Physiological studies	Analytical methods and residues	Counteraction	Mammalian safety — acute, subacute, chronic toxicity	Mammalian safety — developmental problems	Submissions to FDA or EPA[a]	Comment or situation[a]
Sodium chloride	c	c	c	c	c	c	c	c	c	c	GRAS
Sulfamerazine	c	c	c	c	c	c	c	c	c	c	Registered for food fish
Terramycin	c	c	c	c	c	c	c	c	c	c	Registered for food fish
Herbicides and algicides											
Copper sulfate	c	c	c	c	c	c	pc	c	c	c	Registered for food fish
2,4-D	c	c	c	c	c	c	pc	c	c	c	Restricted registration
Dichlobenil	c	c	c	c	c	pc	pc	c	pc	c	Nonfood use only
Diquat	c	c	c	c	c	c	c	c	pc	c	Registered for food fish
Diuron	c	c	c	c	c	c	pc	c	pc	o	Registered for irrigation ditches only
Endothall	c	c	c	c	c	c	pc	c	c	c	Registered for food fish
Fenac	c	c	c	c	c	c	o	c	o	c	Nonfood use only
Silvex	c	c	c	c	c	c	pc	c	o	c	Nonfood use only
Simazine	c	c	c	c	c	c	pc	c	pc	c	Registered for food fish
Anesthetics											
MS-222	c	o	c	c	c	c	c	c	c	c	Registered by FDA
Quinaldine sulfate	c	o	pc	c	c	c	o	pc	o	c	Awaiting final action by FDA

[a]Abbreviations: EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = Generally Recognized as Safe; NMFS = National Marine Fisheries Service; RPAR = Rebuttable Presumption Against Registration.

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65. Accumulation and Loss of Residues of 3-Trifluoromethyl-4-nitrophenol (TFM) in Fish Muscle Tissue: Laboratory Studies, by J. B. Sills and J. L. Allen. 1975. 10 pp.
66. Residues of 3-Trifluoromethyl-4-nitrophenol (TFM) in a Stream Ecosystem after Treatment for Control of Sea Lampreys, by P. A. Gilderhus, J. B. Sills, and J. L. Allen. 1975. 7 pp.
67. Method for Assessment of Toxicity or Efficacy of Mixtures of Chemicals, by L. L. Marking and V. K. Dawson. 1975. 7 pp.
68. Development and Evaluation of On-site Toxicity Test Procedures for Fishery Investigations, by R. M. Burress. 1975. 8 pp.

(Reports 69 and 70 are in one cover.)

69. Toxicity of 3-trifluoromethyl-4-nitrophenol (TFM), 2'5,-dichloro-4'-nitrosalicylanilide (Bayer 73), and a 98:2 Mixture to Fingerlings of Seven Fish Species and to Eggs and Fry of Coho Salmon, by T. D. Bills and L. L. Marking. 1976. 9 pp.
70. The Freshwater Mussel (*Anodonta* sp.) as an Indicator of Environmental Levels of 3-trifluoromethyl-4-nitrophenol (TFM), by A. W. Maki and H. E. Johnson. 1976. 5 pp.
71. Field Tests of Isobornyl Thiocyanoacetate (Thanite) for Live Collection of Fishes, by R. M. Burress, P. A. Gilderhus, and K. B. Cumming. 1976. 13 pp.
72. Toxicity of Rotenone to Fish in Standardized Laboratory Tests, by L. L. Marking and T. D. Bills. 1976. 11 pp.

(Reports 73 through 76 are in one cover.)

73. Formalin: Its Toxicity to Nontarget Aquatic Organisms, Persistence, and Counteraction, by T. D. Bills, L. L. Marking, and J. H. Chandler, Jr. 1977. 7 pp.
74. Chlorine: Its Toxicity to Fish and Detoxification of Antimycin, by L. L. Marking and T. D. Bills. 1977. 5 pp.
75. Malachite Green: Its Toxicity to Aquatic Organisms, Persistence, and Removal with Activated Carbon, by T. D. Bills, L. L. Marking, and J. H. Chandler, Jr. 1977. 6 pp.
76. Toxicity of Furanace to Fish, Aquatic Invertebrates, and Frog Eggs and Larvae, by L. L. Marking, T. D. Bills, and J. H. Chandler, Jr. 1977. 6 pp.

(Reports 77 through 79 are in one cover.)

77. Efficacy of 3-Trifluoromethyl-4-nitrophenol (TFM), 2',5-Dichloro-4'-nitrosalicylanilide (Bayer 73), and a 98:2 Mixture as Lampricides in Laboratory Studies, by V. K. Dawson, K. B. Cumming, and P. A. Gilderhus. 1977. 11 pp.
78. Toxicity of the Molluscicide Bayer 73 and Residue Dynamics of Bayer 2353 in Aquatic Invertebrates, by H. O. Sanders. 1977. 7 pp.
79. Accumulation, Elimination, and Biotransformation of the Lampricide 2',5-Dichloro-4'-nitrosalicylanilide by *Chironomus tentans,* by J. A. Kawatski and A. E. Zittel. 1977. 8 pp.

(Reports 80 and 81 are in one cover.)

80. Effects of Antimycin A and Rotenone on Macrobenthos in Ponds, by L. J. Houf and R. S. Campbell. 1977. 29 pp.
81. Aquatic Macroinvertebrates in a Small Wisconsin Trout Stream Before, During, and Two Years After Treatment with the Fish Toxicant Antimycin, by G. Z. Jacobi and D. J. Degan. 1977. 24 pp.

82. *Investigations in Fish Control:* Index to Numbers 1–72, 1964–76, by R. A. Schnick and K. A. Graves. 1977. 19 pp.

(Reports 83 through 85 are in one cover.)

83. Survival of Two Species of Freshwater Clams, *Corbicula leana* and *Magnonaias boykiniana,* After Exposure to Antimycin, by L. L. Marking and J. H. Chandler, Jr. 1978. 5 pp.
84. Chronic and Simulated Use-Pattern Exposures of Brook Trout (*Salvelinus fontinalis*) to 3-Trifluoromethyl-4-nitrophenol (TFM), by W. P. Dwyer, F. L. Mayer, J. L. Allen, and D. R. Buckler. 1978. 6 pp.
85. Hydrolysis and Photolysis of the Lampricide 2',5-Dichloro-4'-nitrosalicylanilide (Bayer 73), by D. P. Schultz and P. D. Harman. 1978. 5 pp.

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